COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets

(hydroxychloroquine sulfate)

NL/H/5194/001/DC

Date: 12 August 2020

This module reflects the scientific discussion for the approval of Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets. The procedure was finalised at 24 June 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets from Intas Third Party Sales 2005, S.L.

The product is indicated in adults for:

- for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and photodermatoses
- for prevention and treatment of uncomplicated malaria caused by *Plasmodium vivax*, *P. ovale*, *P. malariae* and chloroquine sensitive *P. falciparum*

The product is indicated in the paediatric population (≥6 years and ≥31 kg) for:

- Treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.
- prevention and treatment of uncomplicated malaria, caused by *Plasmodium vivax*, *P. malariae*, *P. ovale* and chloroquine-sensitive *P. falciparum*.

Chloroquine-resistant *P. falciparum*, and increasingly chloroquine-resistant *P. vivax*, occur in many regions, which limits the usability of hydroxychloroquine in these regions.
Official guidelines and local information about the occurrence of anti-malarial drug resistance need to be taken into account. Examples of this include WHO and public safety guidelines.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Plaquenil 200 mg film-coated tablets which has been registered in Denmark by Sanofi-Aventis Denmark A/S since 5 May 1958. In the Netherlands, Plaquenil 200 mg film-coated tablets has been registered since 21 November 1966 (NL License RVG 00853).

The concerned member states (CMS) involved in this procedure were Germany, Poland and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product is a white to off-white, peanut shaped, biconvex, film-coated tablet debossed with “H11” on one side and plain on the other side.

Each film-coated tablet contains 200 mg of hydroxychloroquine sulfate.

The product is packed in transparent PVC/aluminium foil blister packs.

The excipients are:
tablet core – lactose monohydrate, maize starch, povidone (E1202) and magnesium stearate (E470b)
tablet coating – polyvinyl alcohol (E1203), talc (E553b), macrogol and titanium dioxide (E171).

II.2 Drug Substance

The active substance is hydroxychloroquine sulfate an established active substance described in the European Pharmacopoeia (Ph. Eur.). It is a white or almost white crystalline powder. The active substance is a BCS class III compound, which is freely soluble in water but practically insoluble in other solvents (95 % ethanol and ether). It contains a chiral carbon and can exhibit optical isomerism. However, the substance is produced as racemate. Two polymorphic forms exist which have different melting point (198 °C and 242 °C). The drug substance used in the drug product corresponds to the second polymorphic form (melting point 240 °C or more).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph. Eur. with additional requirements indicated on

the CEP. Furthermore, tests for particle size distribution and microbial quality have been included. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Several development studies have been performed related to the characterisation of reference product, choice and quantity of the excipients, choice of the manufacturing formula and *in vitro* comparative study with the reference product. A bioequivalence study versus the EU reference product Plaquenil 200 mg Film-coated tablets has been performed. The drug product batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process uses a wet granulation method and consists of granulation, blending and lubrication, compression and film-coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the European Pharmacopoeia (Ph.Eur.). These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, loss on drying, resistance to crushing of tablets, uniformity of dosage units, assay, related substances and microbial quality. The release and shelf-life requirements/limits are aligned. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three full-scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (12 months). The conditions used in the stability

studies are according to the ICH stability guideline. No significant changes are observed in any of the parameters tested. The drug product remains stable throughout the test period. The proposed shelf-life of 30 months, without any special storage conditions, is justified.

Photostability testing was performed on the drug product according to ICH Guidelines for direct exposure and in the blister packaging as proposed for marketing. It can be concluded from the study that the drug product is photo-stable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. One post-approval commitment was made:

- The MAH committed to perform hold time study for film-coated tablets up to 120 days on first two commercial scale batches to support the hold time of 115 days for film coated tablets. Further, they confirmed that during hold time study new batches will be evaluated with revised dissolution limit (NLT 80 % (Q) in 15 minutes). The results of the hold time study will be submitted for review by 9 November 2020.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Plaquenil which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydroxychloroquine sulfate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets (Intas Third Party Sales 2005, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Plaquenil 200 mg film-coated tablets (Sanofi Aventis, Denmark).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

An open label, randomised, single-period, two-treatment, parallel, balanced, single dose bioequivalence study was carried out in 148 healthy male subjects, aged 18-44 years. 74 subjects were included in each arm. Each subject received a single dose (200 mg) of one of the two hydroxychloroquine formulations. The tablet was orally administered with 240 ml water 30 minutes after serving of standardised high-calorie and high-fat vegetarian breakfast. There was one dosing period. As this study had a parallel study design, no washout period was necessary.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 7, 8, 10, 12, 16, 20, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A parallel design was chosen, as the elimination half-life of hydroxychloroquine is very long (about 50 days)

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Three subjects were withdrawn from the study as they did not consume the required amount of breakfast and two were replaced by two standby subjects. One subject was withdrawn due to vomiting prior to dosing and one subject had an episode of giddiness prior to dosing and was withdrawn from the study on medical grounds. Two subjects discontinued from the study on their own accord after dosing. Four subjects did not want to continue the study and two were replaced by standby subjects. Therefore, a total of 137 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydroxychloroquine under fed conditions.

Treatment N=67 (test) n=70 (reference)	**AUC_{0-72h} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	4821 ± 1678	248 ± 92	5.5 (1.33 – 7.0)
Reference	4596 ± 1250	223 ± 68	5.5 (2.0 – 8.0)
*Ratio (90% CI)	1.04 (0.95 – 1.13)	1.10 (1.00 – 1.21)	--
CV (%)	32.4	35.1	--

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets is considered bioequivalent with Plaquenil 200 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Hydroxychloroquinesulfaat Edest.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Overdose - Severe hypoglycaemia - Visual disturbance - Gastrointestinal effects
Important potential risks	- Patients with hepatic and renal insufficiency - Cardiac conduction disorders - Haematological effects - Musculoskeletal effects - Medical dermatitis - Use in pregnancy - Use in breastfeeding
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Plaquenil. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Plaquenil 200 mg film-coated tablets (content) and Intas 5 mg and 10 mg orodispersible tablets (layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Hydroxychloroquinesulfaat Edest 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Plaquenil 200 mg film-coated tablets. Plaquenil is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hydroxychloroquinesulfaat Edest with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 January 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse